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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,135	04/11/2007	Ifor Delme Bowen	000487.00042	6308

22907 7590 03/03/2010

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EXAMINER	
MI, QIUWEN	

ART UNIT	PAPER NUMBER
1655	

MAIL DATE	DELIVERY MODE
03/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,135	BOWEN ET AL.	
	Examiner	Art Unit	
	QIUWEN MI	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-9* is/are pending in the application.

4a) Of the above claim(s) *3,6,7 and 9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,5 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 May 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment in the reply filed on 1/27/2010 is acknowledged, with the cancellation of Claims 1, 10, and 11. Claims 2-9 are pending. Claims 3, 6, 7, and 9 are withdrawn. **Claims 2, 4, 5, and 8 are examined on the merits.**

Claim Rejection 112, 1st

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2, 4, 5, and 8 are newly rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting cancer cell growth in vitro, does not reasonably provide enablement for treating cancer, which encompasses treating cancer in vivo or treating cancer in a human subject. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature or the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the relative skill of those in the art; (5) the predictability or unpredictability of the art; (6) the amount of direction or guidance presented; (7)

the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention is drawn to a method for treating cancer comprising administering to a patient in need of such treatment an effective dose of a compound, wherein the compound is a terpene selected from the group consisting of trans-beta-ocimene; and gamma-risabolene.

Merck Manual indicates a cancer is an abnormal growth of cells (usually derived from a single cell). The cells have lost normal control mechanisms and thus are able to expand continuously, invade adjacent tissues, migrate to distant parts of the body, and promote the growth of new blood vessels from which the cells derive nutrients. Cancerous (malignant) cells can develop from any tissue within the body. As cancerous cells grow and multiply, they form a mass of cancerous tissue—called a tumor—that invades and destroys normal adjacent tissues. The term tumor refers to an abnormal growth or mass. Tumors can be cancerous or noncancerous. Cancerous cells from the primary (initial) site can spread throughout the body (metastasize) (see Introduction of cancer from Merck Manual, accessed on 2/23/2010, pp 1-3).

(2) the breadth of the claims:

The invention is drawn to a method for treating cancer comprising administering to a patient in need of such treatment an effective dose of a compound, wherein the compound is a terpene selected from the group consisting of trans-beta-ocimene; and gamma-risabolene. Thus, the breadth of the claims encompasses administering to a subject who is suffering from cancer an

effective amount of gamma-risabolene. As evidenced by Appel et al (Appel et al, Metabolic stability of experimental chemotherapeutic agents in hepatocyte:tumor cell co-cultures, Cancer chemotherapy and pharmacology, (1986) Vol. 17, No. 1, pp. 47-52), A U.S. National Cancer Institute screening program for new anticancer drugs, based on the growth of primary human tumor cells in an in vitro soft agar colony formation assay, has resulted in the identification of a number of compounds that have cytotoxic activity against primary human tumor cells in vitro but are inactive in the conventional in vivo murine P388 leukemia animal model pre-screen (see Abstract).

(3) the state of the art:

Those of skill in the art recognize that in vitro assays and or cell-cultured based assays are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in- vitro assay does not permit a single extrapolation of in vitro assays to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore it is well known in the art that cultured cells, over a period time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Freshney, Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell

interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro)*. Further, Dermer (Dermer, Another anniversary for the war on cancer, Bio/Technology, 1994, 12:320) teaches that, "petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interactions.

Therefore, there is a discrepancy between inhibiting cancer cell growth in vitro and treating cancer in vivo or in a human subject.

(4) the relative skill of those in the art

The relative skill in the art is high. The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g.M.D., Ph.D., Pharm. D. or combinations thereof).

(5) The predictability or unpredictability of the art:

Treatment of cancer in general is at most unpredictable, as underscored by Gura (Gura, Science, v278, 1997, pp. 1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive. Fredyc et al (Fredyc et al, Cytotoxic flavone analogues of vitexicarpin, a constituent of the leaves of Vitex negundo, Journal of natural products, (2003 Jun) Vol. 66, No. 6, pp. 865-7) teach bioassay-guided fractionation of the chloroform-soluble extract of the leaves of Vitex negundo led to the isolation of the known flavone vitexicarpin (1), which exhibited broad cytotoxicity in a human cancer cell line panel. In an attempt to increase the cytotoxic potency of 1, a series of acylation reactions was performed on this compound to obtain its methylated (2), acetylated (3), and six new acylated (4-9) derivatives. Compound 9, the previously unreported 5,3'-dihexanoyloxy-3,6,7,4'-tetramethoxyflavone, showed comparative cytotoxic potency to compound 1 and was selected for further evaluation. However, this compound was found to be inactive when evaluated in the in vivo hollow fiber assay with Lu1, KB, and LNCaP cells at the highest dose (40 mg/kg/body weight) tested, and in the in vivo

P-388 leukemia model (135 mg/kg), using the ip administration route (see Abstract). Further more, Mamber et al (Mamber et al, Biological effects of acetomycin. I. Activity against tumor cells in vitro and in vivo, Journal of Antibiotics, (1987) Vol. 40, No. 1, pp. 73-76) teach The antibiotic acetomycin was active in vitro against HCT-8 human colon adenocarcinoma cells (IC50, 1.5 .mu.g/ml) and L1210 murine leukemia cells (IC50, 2.2 .mu.g/ml). Acetomycin also had marked activity in the human tumor stem cell assay, with a 33% overall response rate (.ltoreq.30% survival) against 49 primary tumors. However, acetomycin was inactive in four in vivo tumor assay systems (L1210 and P388 leukemias, B16 melanoma and the MX-1 mammary xenograft system). This lack of in vivo activity may result from metabolic inactivation of acetomycin (see Abstract).

Since treating cancer in vivo or in a human subject is such a complex issue, the state of the art has not been able to predict whether the in vitro data would be consistent with animal model or clinical trials, the predictability of the art is very low.

(6) The amount of direction or guidance presented.

Regarding cancer treatment, the specification provides cytotoxicity data of ethanol extract of C. molmol, trans-beta-ocimene, gamma-bisabolene, and alpha-bisabolol in cancer cell lines S180, HT1080, MM6, A375 and apoptotic effect of ethanol extract of C. molmol using Annexin V binding assay. However, the specification has not provided guidance on administering the claimed compound to any patient, neither to an animal or a human.

(7) The presence or absence of working examples.

Regarding cancer treatment, the specification provides examples regarding cytotoxicity data of ethanol extract of C. molmol, trans-beta-ocimene, gamma-bisabolene, and alpha-bisabolol in cancer cell lines S180, HT1080, MM6, A375 and apoptotic effect of ethanol extract of C. molmol using Annexin V binding assay. However, the specification has not provided working examples on administering the claimed compound to any patient, neither to an animal or a human.

(8) The quantity of experimentation necessary:

Since treating cancer in vivo or in a human subject is such a complex issue, the state of the art has not been able to the state of the art has not been able to predict whether the in vitro data would be consistent with animal model or clinical trials outcomes. Plus none of the claimed compound has been able to treat cancer in vivo or in human subject, and the specification has not provided any guidance regarding treating cancer in vivo or in human using any of the claimed compound, the quantity of experimentation is undue and the result is unpredictable. Further more, in order to treat cancer, the treatment regimen must be identified, and the end point of the treatment also needs to be identified. Since the Applicant have not provided the appropriate time frame at which the compound should be administered to treat cancer, the effective dosage of in vivo or in human clinical trials, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine if the compound would be effective in treating cancer.

Based on the aforementioned reasons the Examiner concludes that the specification, while being enabling for inhibiting cancer cell growth in vitro, does not reasonably provide enablement for the treat cancer in vivo or in human subject without requiring the ordinary skilled

artisan to undertake undue experimentation. Since the state of the art is highly unpredictable and requires much greater guidance for an ordinary skilled artisan to effectively treat cancer, burdensome experimentation, such as animal models or clinical studies would necessarily be required of the ordinary skilled artisan to establish the treatment of cancer.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Qiuwen Mi whose telephone number is 571-272-5984. The examiner can normally be reached on 8 to 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on 571-272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Qiuwen Mi/

Examiner, Art Unit 1655